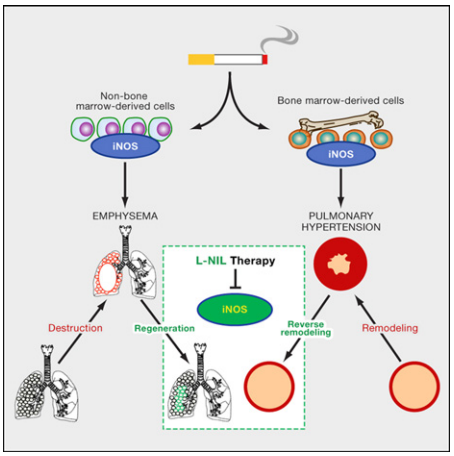
In This Issue

Cell



iNOS Inhibitors Clear the Smoke

PAGE 293

Using mice chronically exposed to tobacco smoke, Seimetz et al. show that inducible nitric oxide synthase (iNOS) plays a role in the development of two lung diseases associated with smoking, emphysema and pulmonary hypertension. Knockout of iNOS protects the mice against these chronic diseases, whereas treatment of tobacco-exposed wild-type mice with an iNOS inhibitor prevents and even reverses established lung disease.

Breaking Bcr-Abl Resistance in Leukemia

PAGE 306

The oncogenic fusion protein Bcr-Abl is a constitutively active tyrosine kinase that initiates chronic myeloid leukemia. Although specific tyrosine kinase inhibitors exist, resistance mutants eventually arise, reducing the clinical usefulness of such drugs. Grebien et al. now identify an intramolecular interface within the Bcr-Abl protein that is essential for oncogenic activity. Disruption of the interface not only prevents leukemia formation in mice, but also enhances the effectiveness of tyrosine kinase inhibitors against resistant Bcr-Abl mutants.

Spooky Intron Action

PAGE 320

Most yeast introns are found in duplicated ribosomal protein (RP) genes. Parenteau et al. examine the functional contribution of these introns and find that deleting an intron from one paralog modifies the expression of both RP paralogs. The intron-dependent change in RNA expression alters cell fitness and response to stress, showing that introns can control optimal expression and function of RP genes.

STING Steers STAT Signaling

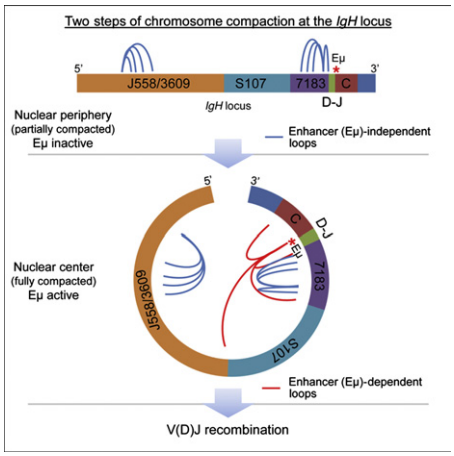
PAGE 447

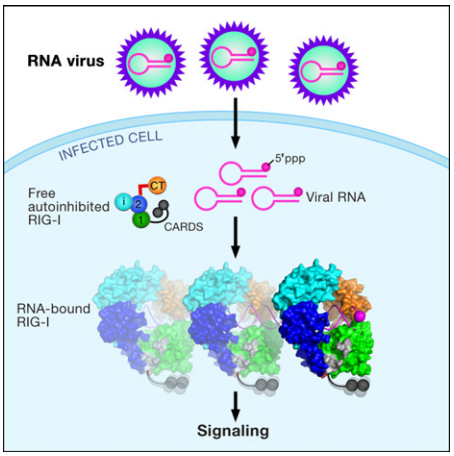
JAK/STAT signaling mediates adaptive immunity by controlling transcription in response to cytokines. Chen et al. now show that STAT6 is also activated directly by virus-sensing platforms at the endoplasmic reticulum, independently of JAK. Viral nucleic acids trigger STING (also known as ERIS/MITA) to recruit STAT6, facilitating its phosphorylation by TBK1 and promoting the expression of distinct target genes required for antiviral innate immunity.

Enhancers Stitch It Up

PAGE 332

Changes in nuclear positioning and chromatin compaction at the immunoglobulin heavy-chain (*IgH*) locus are required prior to recombination. Guo et al. demonstrate that the conformation of this huge locus is generated in two enhancer-mediated steps. In the first step, the Eμ enhancer reconfigures the locus into several multilooped domains. Then, Eμ brings these domains together to generate a compacted structure in which the ends are in spatial proximity.





RIG-I Wriggles 'Round Viral RNA

PAGE 409 and PAGE 423

RIG-I recognizes viral dsRNA within host cells and initiates an innate immune response. Two papers in this issue provide detailed structural and mechanistic insights into this recognition event. Luo et al. report the structure of RIG-I, lacking the N-terminal CARD domains, in complex with dsRNA, showing how the protein wraps around the RNA and how the organization within the complex supports RIG-I multimerization. In a series of structures including full-length RIG-I, Kowalinski et al. provide insight into the conformational changes that occur as RIG-I binds viral RNA and ATP to trigger signaling through the CARD domains. Together, these studies illuminate key steps leading to stimulation of an interferon response to infection.

ceRNAs Soak Up Oncogenic MicroRNAs

PAGE 344, PAGE 370, and PAGE 382

Individual genes often contain binding sites for multiple microRNAs, and conversely, individual microRNAs often target multiple RNA transcripts. Now, three studies identify a large regulatory network of RNA transcripts that controls the tumor suppressor PTEN by sequestering its microRNAs. Tay et al. and Sumazin et al. demonstrate that ~20 of these "competitive endogenous RNAs" (ceRNAs) exhibit tumor suppressor activity in multiple types of cancers, and Karreth et al. discover a PTEN ceRNA that, when lost, cooperates with oncogenic BRAF to promote melanoma in a mouse model. Independently, Semuzin et al. also develop a computational tool that uncovers ~7,000 putative ceRNAs, mediating hundreds of thousands of pair-wise gene interactions in glioblastoma.

ceRNA LINC to Muscular Dystrophy

PAGE 358

Cesana et al. discover a long noncoding RNA, linc-MD1, that governs muscle cell differentiation by competitively binding to microRNAs that target muscle-specific transcription factors. Linc-MD1 acts as a decoy, or "competitive endogenous RNA" (ceRNA), modulating the availability of these microRNAs. Interestingly, linc-MD1 also functions as the pri-miRNA for miR-133b, and linc-MD1 levels are strongly reduced in Duchenne muscle cells.

Pain Relief without the Itch

PAGE 447

Itch is a common side effect of opioid-mediated pain relief. Liu et al. now reveal that sensations of itch or pain can be molecularly uncoupled. They provide evidence that opioid-induced itch is mediated only by neurons expressing heteromers of a specific isoform of the m-opioid receptor (MOR) with the gastrin-releasing peptide receptor. A distinct, differentially expressed MOR isoform mediates analgesia. These findings provide a therapeutic target for separating analgesia from the side effects of itch.

Networks Built by Node Breakdown

PAGE 459

Emanuele et al. use two complementary approaches to identify nearly 500 Cullin-RING ubiquitin ligase substrates. This collection is enriched for proteins at highly connected nodes within interaction networks, indicating that proteolysis substrates are positioned to maximally impact information flow.

RF-ereeing Protein Fidelity

PAGE 396

Zaher et al. show that the *E. coli* translation release factor RF3, previously thought to play a role in the recycling of other release factors, plays an essential proofreading role in ensuring translational fidelity in vivo. The authors show that RF3 promotes premature termination when peptides contain errors. Protein yields increase in the absence of RF3 but at the expense of fidelity.